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Original Research Paper

Serum Bilirubin and C-Reactive Protein as Predictor of Perforation in Acute Appendicitis- A Prospective Cohort Study

Surgery

KEYWORDS : serum bilirubin, C- reactive protein, appendicitis, appendicular perforation.

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ABSTRACT

Introduction- *Acute appendicitis is a common surgical emergency, further complicated by gangrene, perforation and diffuse peritonitis. An early diagnosis and treatment of perforated appendix can decrease cost as well as morbidity associated with the disease. Total Serum Bilirubin (TSB) and C-reactive protein (CRP) can be potential markers to predict perforation in patients with acute appendicitis.*

Method- *TSB and CRP were measured in patients with acute appendicitis. Patients were divided into two groups- group 1 (without appendicular perforation) and group 2 (with appendicular perforation) on the basis of operative findings. Sensitivity, Specificity, Positive predictive value (PPV) and Negative predictive value (NPV) were calculated for both parameters.*

Results- *The sensitivity, specificity, PPV and NPV of raised TSB in Group 2 were 86.66%, 65.71%, 72.22% and 92% respectively. The sensitivity, specificity, PPV and NPV for CRP was 80.0%, 54.28%, 38.7%and 84% respectively. TSB was found to be a better marker for diagnosing perforated appendix than CRP.*

Conclusion- *Both TSB and CRP are useful markers for early diagnosis of perforated appendix, with TSB being better than CRP. But, the present study has a limitation with respect to sample size.*

Introduction

Acute appendicitis (AA) is one of the most commonly encountered intra-abdominal affections seen in surgical emergency and can be treated easily if accurate diagnosis is made on time. A delay in diagnosis and treatment can lead to catastrophic complications e.g. Gangrene, perforation and diffuse peritonitis [1]. Its diagnosis is usually made on the basis of presenting history, clinical examination and laboratory tests, with an accuracy of 76% to 92%. Negative appendectomy rate solely on the basis of clinical diagnosis still ranges between 15 to 25% [2,3].

Appendectomy, like any other operation, results in socio-economic impacts in the form of lost working days and declined productivity [3]. The incidence of perforated appendicitis in adults has been reported from 13-37% or higher. Perforated appendicitis has been associated with early and long term complication, hence early diagnosis and treatment is important [4].

Hyperbilirubinemia is the result of imbalance between production and excretion of bilirubin by the liver. It may be because of hepatocellular cholestatic or haemolytic diseases. Liver receives blood mainly through portal venous system, which receives blood fromabdominal organs. Portal blood carries nutrients and othersubstances absorbed from gut including bacteria and its product (toxins) to the liver. But when bacterial load, cytokines e.g. IL-6, tumour necrosis factor (TNF), as in acute appendicitis overwhelms the kuffer cell function, they may cause dysfunction or damage to the hepatocytes (liver parenchyma). It reflects as rise in serum bilirubin (SB) alone or in combination with liver enzymes depending upon the type, severity and site of lesion [5].

C-reactive protein (CRP) is a protein found in the blood, the levels of which rise in response to inflammation (i.e. C-reactive protein is an acute-phase protein). Normal concentration in healthy human serum is usually lower than 10 mg/l, slightly increasing with aging. Higher levels are found in late pregnancy, mild inflammation and viral infections (10-40 mg/l), active inflammation, bacterial infection (40-200 mg/l), severe bacterial infections etc. [6].

No reliable specific marker as predictor of perforation in acute appendicitis has been identified, but few recent studies have shown significant role of hyperbilirubinemia and CRP as a predictor of perforation in acute appendicitis **[7,8].**

Thus this study was undertaken to evaluate SB and CRP as predictive factors for perforation in acute appendicitis, to compare between SB and CRP, the better predictor of perforation in acute appendicitis, and to evaluate the specificity, sensitivity and predictive values of each of the parameters in perforated acute appendicitis.

Material and method

This prospective cohort study was conducted on 50 diagnosed cases of acute appendicitis between the period of November 2011 to November 2013 in Jawaharlal Nehru Medical College, AMU, Aligarh in collaboration with interdisciplinary biotechnology unit, AMU, Aligarh.

Clinically suspected cases were subjected to investigations to make the provisional diagnosis. Investigations included total leukocyte count, differential leukocyte counts and ultrasonography. ALVARADO score was the calculated & these cases were also be subjected to routine liver function test (LFT) and levels of serum CRP. Subsequently, diagnosed cases were operated and appendectomy was done. Diagnosis was confirmed per-operatively and post-operatively by histopathological examination. On the basis of operative findings patients were divided into two groups

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group 1 – AA without perforation, and group 2 - AA with perforation.

Exclusion criteria
Patients with normal appendix found per-operatively and on histopathology.
Patients with hepato-biliary disease.

Patients with other infective conditions.

Measurement of serum- CRP:After the blood was collected, the serum was separated by centrifugation and stored in sterile vials at freezing temperature (-20°C). After the samples were collected CRP values in each serum sample were estimated using CRP kit (by ELISA technique).Normal range of CRP was taken as <60mg/L.

Normal range of total serum bilirubin (TSB) was **taken from 0-1.2mg/100ml.**

Normal range of total leucocyte count in our lab was **4500-11000 cells/uL.**

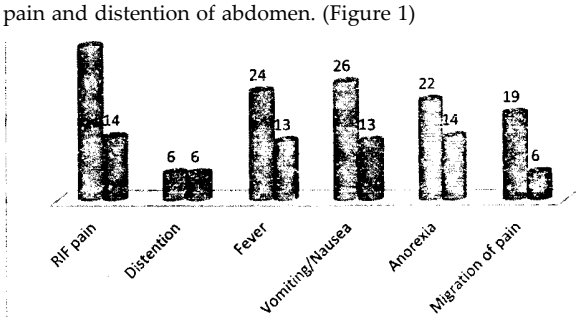
Student t-test was used for statistical analysis. A p value of <0.05 was considered statistically significant.

Results
Total of 50 cases of acute appendicitis were studied from November 2011 to November 2013. The ages of the patients **varied from 10 years to 65 years** with a **mean** age of 25.5± S.D 13.2 years. Most of the patients in our study were in the age group of10 to 20 years which consists 50% patients. The male accounted for 64% (32) patients and the female for 36% (18) of the study population. The male to female ratio was 1.77:1.

Table 1:Sex distribution in two groups

Sex	Group 1	Group 2
Male	24(68.57)	8(53.33)
Female	11(31.42)	7(46.66)

Majority of the patients (58%) in our study presented within 24 hours of the onset of symptoms.96% (48) patients presented with RIF pain. Other common presenting complaints were vomiting/nausea, fever, anorexia, migrating pain and distention of abdomen. (Figure 1)



RIF tenderness was the most common clinical sign among the study population accounting for 98% (49) patients. Other common clinical signs includes rebound tenderness, generalized abdominal tenderness.

The pre-operative total leucocyte count was raised in 45.71 % (16) of the patients in the group 1 and was raised in 80% (12) of the patients in group 2. 57.14% (20) of patients in the group 1 had raised neutrophil counts (i.e.> 75%) while in the group 2, 73.33 % (11) of patients had raised neutrophil count.

In our study 38% patients had an ALVARADO'S score in the range 5 - 6 , 40% in the range 7 - 8 and 22%> had their score 9-10. In the group 1, 45.71% patients had ALVARADO score in the range 5 - 6 , 37.14% in the range 7 - 8 and 17.14% 9-10. In the group 2, 20% patients had ALVARADO score in the range of 5 - 6, 46.66% in the range 7 - 8 and 33.33% had their score 9 - 10.

50% of the total patients in our study had an increase in total serum bilirubin (>1.2mg/100ml). 34.28% (12) patients in the group 1had increased total serum bilirubin (TSB) while in group 2, 86.66% (13) patients had an increase in TSB and the difference between the two was statistically significant (Table 2).

56% (28) of the total patients in our study had an increase in serum C- reactive protein (>60mg/l). 45.71% (16) patients in the group of acute appendicitis without perforation had increased serum C- reactive protein (CRP) while in the group of acute appendicitis with perforation 80% (12) patients had an increase in CRP and the difference was statistically significant between the two. (Table 2)

TABLE 2: TSB and CRP in two groups.

Table 12: TSB & CRP two groups of patients.

Tests	Acute appendicitis without perforation N=35(%)	Acute appendicitis with perforation N=15 (%)	Total N= (%)	Chi square value	Degree of freedom	P-value*
TSB						
(>1.2mg/100ml)						
Present	12(34.28)	13 (86.66)	25 (50)	11.5	1 /	0.001
Absent	23(65.7 i)	2(13.33)	25 (50)			
Serum CRP						
(> 60 mg/1)			28			
Present	16(45.71)	12(80)	(56)			
Absent	19(54.28)	3(20)	22 (44)	5.01 *	1	0.025

* Chi square test.

The sensitivity of increase in TSB in Group 2 in our study was 86.66%. The specificity of the test was found to be 65.71%. The positive predictive value and negative predictive value of the test, in our study was 72.22% and 92% respectively (table 3).

Table 3: Sensitivity and specificity of total serum bilirubin in predicting perforation

(TSB>1.2/dL)	Perforation		Sensitivity (%)	Specificity (%)	PPV(%)	NPV(%)
	Present	Absent				
+ve	13	12	86.66	65.71	72.22	92
-ve	2	23				

The sensitivity and specificity of group 2 for CRP was 80.0% & 54.28%respectively. The positive predictive value and negative predictive value of the test, in our study was found to be 38.7%and 84%respectively. (table 4)

Table 4: Sensitivity and specificity of CRP in predicting perforation

(CRP>60mg/l)	Perforation		Sensitivity (%)	Specificity (%)	PPV(%)	NPV(%)
	Present	Absent				

+ve	12	19	80.00	54.28	38.7	84
-ve	3	16				

Discussion

Acute appendicitis **is one of the most common** surgical conditions encountered in **surgical practice and at times maybe a** cause of mortality.The **aims and objectives of the study** were to evaluate total serum bilirubin (TSB) **and C - reactive protein** (CRP) individually as predictor of **perforation in acute appendicitis and** also to compare both in terms of **sensitivity, specificity, positive** predictive value and negative predictive **value as predictor of perforation** in acute appendicitis.

50% of patients of our study population **had elevated total serum bilirubin** level. This finding is lower than a **study by Khan S** in **2006 who** documented the incidence of elevated **serum bilirubin to be** as high as 86.6%. In another study by **Khan** S in **2008, the incidence of** elevated **TSB was** found to be **82.07% [1, 9].**

Our findings are almost similar to previous report by Von Titte, et al who documented a high incidence of elevated serum bilirubin in cases of acute appendicitis [10]. In a prospective study involving 45 patients, authors concluded that hyperbilirubinemia may be used in diagnosis of AA [9].

In the group 1, elevated serum bilirubin was present in 34.28% patients and in the group 2, it was present in 86.66% patients. Significant difference was noted between the two groups ($p < 0.05$). Estrada JJ, et al in their study state "we have found that in a series of patients with acute appendicitis, hyperbilirubinemia was found in well over one third of all patients, and in more than half of the patients with a perforated appendix". They stated that hyperbilirubinemia is an independent predictor of appendicular perforation, with nearly a 3 fold risk of perforated appendicitis in patients with increased total bilirubin levels [11]. Hyperbilirubinemia has been shown to correlate with a diagnosis of perforated appendicitis [11]. A raised SB level is a good indicator of complicated acute appendicitis and patients with hyperbilirubinaemia are more likely to have Appendiceal perforation or gangrene as also shown by Jamaluddin M, et al [12].Khan **S** in his study concluded that in complicated acute appendicitis (gangrenous and perforation) total serum bilirubin was more elevated than in simple suppurative acute appendicitis [1].

The sensitivity of elevated serum bilirubin in our study was found to be 86.66%, the specificity 65.71%, positive predictive value was found to be 72.22% and the negative predictive value was 92%. Following table shows the comparative results of various studies done to evaluate TSB as predictor of perforation in acute appendicitis [4, 11, 13, 14].

STUDIES	**SENSITIVITY** (%)	**SPECIFICITY** (%)	**PPV*** (%)	**NPV**** (%)
Estrada, et al.	56	31	39	82
Beltran MA, et al.	57	57	-	-
Atahan k, et al.	78	87	46	97
Giordano s, et al.	45	82	-	-
Present study	86.66	65.71	72.22	92

***Positive Predictive Value;**Negative Predictive Value**

C- Reactive Protein:

There have been many reports emphasizing the value of CRP in improving the diagnostic accuracy of acute appendicitis but very few studies have studied CRP as predictor of perforation in acute appendicitis. In our study population, elevated serum CRP was present in 56% patients. Our finding of high incidence of increase in CRP was consistent with previous study by Oosterhuis et al. who documented high incidence (87%) of elevated serum CRP in cases of acute appendicitis and also showed that serial CRP measurement could improve the accuracy of diagnosing acute appendicitis. The higher value of CRP in the diagnosis of acute appendicitis is also confirmed by Dahmardehei, et al (85%) [15, 16].

In group 1, elevated serum CRP was present in 45.71% patients and in group 2, in 80% patients. Significant difference was noted between the two groups ($p < 0.05$). Our finding is consistent with multiple previous studies which documented a statistically significant difference in elevated CRP, between patients of acute appendicitis with perforation and without perforation [17, 18, 19, 20, 21, 22] .

Beltran et al in their study demonstrated that CRP could differentiate between patients with non-perforated from patients with perforated appendicitis [17]. Yung HR et al reported that an elevated CRP was related to to appendicular perforation, though it could not differentiate between normal appendix and uncomplicated appendicitis [22]. As stated by Kaya B, et al in 2012 "an increase in CRP levels alone is not sufficient to make the diagnosis of acute appendicitis. However, CRP levels may differentiate between phlegmonous appendicitis and perforated appendicitis' [19].

The sensitivity of elevated serum CRP in our study was found to be 80.0%, the specificity 54.28%, positive predictive value was found to be 38.7% and the negative predictive value was 84%. Following is the tabulated comparison of CRP as predictor of perforation in previous studies by various authors [4, 23, 24] :

STUDIES	**SENSTIVITY**	**SPECIFICITY**	**PPV***	NPV**
Beltran MA, et al	**75**	**35**	**-**	-
Kaser SA, et al	**98**	**72**	**18**	**99**
Chaudhary **P,** et al	**100**	**95.2**	**80**	**100**
Present study	**80**	**54**	**39**	**84**

***Positive predictive value;** Negative predictive value**

In various studies sensitivity and specificity ranges from 75%-100% and 35%-96% respectively. In our study sensitivity and specificity lie in the range.

TSB vs CRP

Our study shows serum bilirubin to be a better marker for diagnosing perforated appendix than serum CRP which is similar to previous study by Sand, et al who documented total serum bilirubin to be a better marker for diagnosing appendicular perforation [25].

Tabulated comparative data of sensitivity and specificity of

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CRP and TSB in patients of acute appendicitis with perforation is as follow[4, 23, 24, 25]:

CRP Total Serum Bilirubin

Studies	SESENSITIVITY (%)	SPSPECIFICITY (%)	SESENSITIVITY (%)	SPSPECIFICITY (%)
Beltran MA, et al	57	51	75	35
Sand M, et al	95	35	70	86
Kaser SA, et al	98	72	38	22
Chaudhary P, et al	100	95.2	100	92
Present study	80	54	87	65

Kaser, et al reported a stronger correlation for CRP than serum bilirubin for appendicular perforation in their study, which was in contrast to our study. Chaudhary P, et al also reported CRP to have a better specificity to predict perforation in patients with acute appendicitis.

Conclusion

Thus serum CRP **and total serum bilirubin** (TSB) **can be** used as useful markers for **early diagnosis and prediction** of **perforation in cases of** acute appendicitis. TSB **would be a better marker for early diagnosis** of **perforation** than serum CRP. But, **the present study has a limitation with** respect to sample size and **therefore a larger study is recommended to validate the** present **observations.**

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